REPORT DOCUMENTATION PAGE

Form Approved OMB NO. 0704-0188

1. REPORT DATE (DD-MM-YYYY)	2. REPORT TYPE	3. DATES COVERED (From - To)
02-05-2011	Final Report	1-Feb-2005 - 14-Jun-2010

4. TITLE AND SUBTITLE
Final Report

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W911NF-04-D-0004

5c. PROGRAM ELEMENT NUMBER
611102

6. AUTHORS
Stephen J Lee, Michel R Gagne

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAMES AND ADDRESSES
University of North Carolina - Chapel Hill
Office of Sponsored Research
The University of North Carolina at Chapel Hill
Chapel Hill, NC 27599 -1350

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Research Office
P.O. Box 12211
Research Triangle Park, NC 27709-2211

10. SPONSOR/MONITOR'S ACRONYM(S)
ARO

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
47516-CH-SR.1

12. DISTRIBUTION AVAILIBILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES
The views, opinions and/or findings contained in this report are those of the author(s) and should not contrued as an official Department of the Army position, policy or decision, unless so designated by other documentation.

14. ABSTRACT
The use of dynamic Combinatorial Chemistry to discover, new synthetic receptors is fledgling and its rules remain to be established. This work has articulated how important molecular recognition elements such as h-bonding, aromatic interactions, and especially C-H pi interactions can control how both small molecules and large molecules interact in a recognition scenario.

15. SUBJECT TERMS
molecular recognition

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	15. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			Stephen Lee
UU	UU	UU	UU		19b. TELEPHONE NUMBER 919-549-4365

Report Title

Final Report

ABSTRACT

The use of dynamic Combinatorial Chemistry to discover, new synthetic receptors is fledgling and its rules remain to be established. This work has articulated how important molecular recognition elements such as h-bonding, aromatic interactions, and especially C-H pi interactions can control how both small molecules and large molecules interact in a recognition scenario.

List of papers submitted or published that acknowledge ARO support during this reporting period. List the papers, including journal references, in the following categories:

(a) Papers published in peer-reviewed journals (N/A for none)

"Constitutional, Diastereo- and Enantioselective Amplification of 84-Membered Macrocyclic Hosts for (–)-Cytidine" M. K. Chung, K. Severin, S. J. Lee, M. L. Waters, M. R. Gagné, Chem. Science 2011, 2, 744-747.

"Dynamic Cyclic Thiodepsipeptide Libraries From Thiol-Thioester Exchange" S. Ghosh, L. A. Ingerman, A. Frye, S. J. Lee, M. R. Gagné, M. L. Waters, Org. Lett. 2010, 12, 1860-1863.

"Synthesis of interlocked 56-membered rings by dynamic self-templating" M. K. Chung, P. S. White, S. J. Lee, M. R. Gagné, Angew. Chem. Int. Ed. 2009, 48, 8683-8686.

"Gold(I)-Catalyzed Cascade Cyclization of Allenyl Epoxides" M. A. Tarselli, J. L. Zuccarello, S. J. Lee, M. R. Gagné, Org. Lett. 2009, 11, 3490-3492.

"Sn-Free Ni-Catalyzed Reductive Coupling of Glycosyl Bromides with Activated Alkenes" H. Gong, R. S. Andrews, J. L. Zucarello, S. J. Lee, M. R. Gagné, Org. Lett. 2009, 11, 879-882.

"The Effect of Gas-Phase Reactions on the Quantitation of Cyclic Hydrazone Libraries by Electrospray Ionization (ESI) Mass Spec" H. Schiltz, M.-K. Chung, S. J. Leeb and M. R. Gagné, Org. Biomol. Chem., 2008, 6, 3597-3600.

"Deracemization of a Racemic Dynamic Combinatorial Library Induced by (–)-Cytidine and (–)-2-Thiocytidine" M.-K. Chung, C. M. Hebling, J. W. Jorgenson, K. Severin, S. J. Lee, M. R. Gagné J. Am. Chem. Soc. 2008, 130, 11819-11827.

"Gold(I)-Catalyzed Asymmetric Cycloisomerization of Ene-Allenes into Vinyl-cyclohexenes" M. A. Tarselli, A. R. Chianese, S. J. Lee, M. R. Gagné, Angew. Chem. Int. Ed. 2007, 46, 6670-6673.

"Electrophilic Activation of Alkenes by Pt(II): So Much More Than a Slow Version of Pd(II)" A. R. Chianese, S. J. Lee, M. R. Gagné, Angew. Chem. Int. Ed. 2007, 46, 4042-4059.

"The Discovery of an Enantioselective Receptor for (–)-adenosine from a Racemic Dynamic Combinatorial Library" S. M. Voshell, S. J. Lee, M. R. Gagné, J. Am. Chem. Soc. 2006, 128, 12422-12423.

"Modulating the Activity and Selectivity of an Immobilized Ru-Porphyrin Catalyst using a Fluorous Solvent" E. Burri, S. M. Leeder, K. Severin, M. R. Gagné, Adv. Synth. & Cat. 2006, 348, 1640-1644.

Number of Papers published in peer-reviewed journals: 11.00

(b) Papers published in non-peer-reviewed journals or in conference proceedings (N/A for none)

Number of Papers published in non peer-reviewed journals: 0.00

(c) Presentations

each year at the DTRA S&T Conference

Number of Presentations: 4.00

Non Peer-Reviewed Conference Proceeding publications (other than abstracts):

Number of Non Peer-Reviewed Conference Proceeding publications (other than abstracts): 0

Peer-Reviewed Conference Proceeding publications (other than abstracts):

Number of Peer-Reviewed Conference Proceeding publications (other than abstracts): 0

(d) Manuscripts

Number of Manuscripts: 0.00

Patents Submitted

Patents Awarded

Awards

Graduate Students

NAME	PERCENT_SUPPORTED
Shannon Leeder	1.00
Sharon Voshell	1.00
Steve Andrews	0.25
FTE Equivalent:	**2.25**
Total Number:	**3**

Names of Post Doctorates

NAME	PERCENT_SUPPORTED
Mee-Kyung Chung	0.25
Anthony Chianese	1.00
Luke Zucarello	1.00
FTE Equivalent:	**2.25**
Total Number:	**3**

Names of Faculty Supported

NAME	PERCENT_SUPPORTED	National Academy Member
Michel Gagne	0.00	No
FTE Equivalent:	**0.00**	
Total Number:	**1**	

Names of Under Graduate students supported

NAME	PERCENT SUPPORTED
FTE Equivalent:	
Total Number:	

Student Metrics

This section only applies to graduating undergraduates supported by this agreement in this reporting period

The number of undergraduates funded by this agreement who graduated during this period:	1.00
The number of undergraduates funded by this agreement who graduated during this period with a degree in science, mathematics, engineering, or technology fields:.....	0.00
The number of undergraduates funded by your agreement who graduated during this period and will continue to pursue a graduate or Ph.D. degree in science, mathematics, engineering, or technology fields:.....	1.00
Number of graduating undergraduates who achieved a 3.5 GPA to 4.0 (4.0 max scale):	1.00
Number of graduating undergraduates funded by a DoD funded Center of Excellence grant for Education, Research and Engineering:	0.00
The number of undergraduates funded by your agreement who graduated during this period and intend to work for the Department of Defense	0.00
The number of undergraduates funded by your agreement who graduated during this period and will receive scholarships or fellowships for further studies in science, mathematics, engineering or technology fields:	0.00

Names of Personnel receiving masters degrees

NAME	
Holly Schiltz	
Total Number:	**1**

Names of personnel receiving PHDs

NAME	
Shannon Leeder	
Sharon Voshell	
Total Number:	**2**

Names of other research staff

NAME	PERCENT SUPPORTED
FTE Equivalent:	
Total Number:	

Sub Contractors (DD882)

Inventions (DD882)

Scientific Progress

see attached

Technology Transfer

Final Report

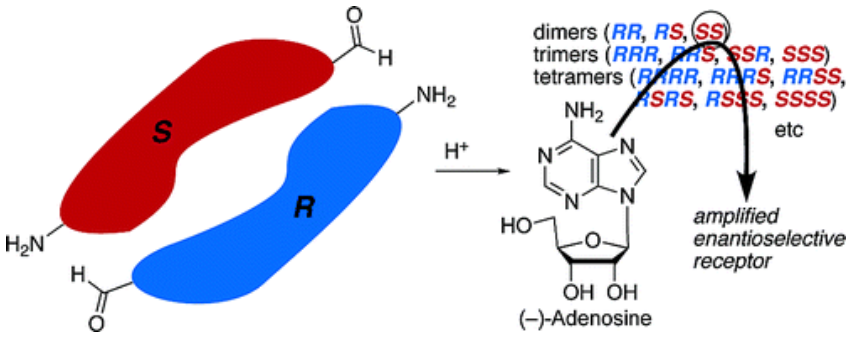
Dr. Stephen J. Lee

W911NF-04-D-0004

Dynamic Combinatorial Chemistry (DCC) is emerging as a new approach to discover synthetic receptors for a broad array of guests. One important reason for its applicability is the fact that the assay is carried out under competitive selection conditions, which causes only the most competent host to be amplified over its competitors. Research efforts have been primarily been focused on articulating the "rules" which describe how this phenomenon presents itself and also utilizes the known methodologies for molecular recognition. When non-obvious strategies are discovered, these situations were examined in more detail. Outlined below are our contributions to the discovery and selection of new molecular receptors for binding and catalysis.

"*The Discovery of an Enantioselective Receptor for (−)-Adenosine from a Racemic Dynamic Combinatorial Library*" Sharon M. Voshell, Stephen J. Lee, and Michel R. Gagné *J. Am. Chem. Soc.*, **2006**, *128*, 12422–12423.

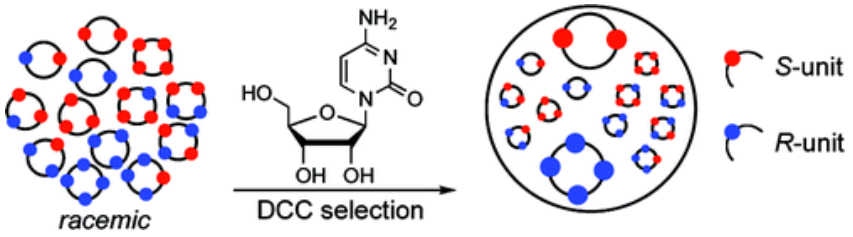
The use of laser polarimetry detection coupled with HPLC is demonstrated to enable the discovery of enantioselective receptors from racemic dynamic combinatorial libraries. Templating with an enantiopure analyte, such as (−)-adenosine, leads to amplification of one enantiomer of the cyclic dimer. A result confirmed with a pseudo-racemic library wherein one of the enantiomers was d-labeled for mass spec analysis. The resulting dimer is thus an enantioselective receptor for (−)-adenosine.



"*Deracemization of a Dynamic Combinatorial Library Induced by (−)-Cytidine and (−)-2-Thiocytidine*" Mee-Kyung Chung, Christine M. Hebling, James W. Jorgenson, Kay Severin, Stephen J. Lee and Michel R. Gagné *J. Am. Chem. Soc.*, **2008**, *130*, 11819–11827.

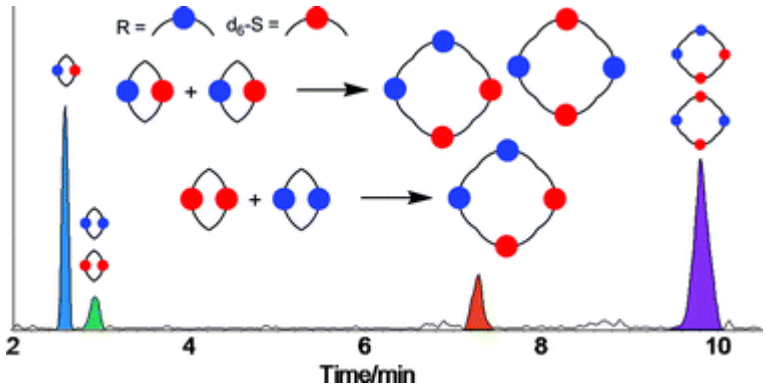
A dynamic combinatorial library composed of racemic hydrazone-based dipeptides becomes deracemized on binding to the chiral analytes (−)-cytidine and (−)-2-thiocytidine through the amplification of two receptors, (*SS*)-dimer and (*RRRR*)-tetramer. The deracemization phenomenon was investigated by laser polarimetry, mass-tagged pseudo-enantiomers in

conjunction with electrospray ionization mass spectrometry, HPLC/UV-MS, UPLC/UV-MS, rapid-resolution LC-MS, collision-induced dissociation MS/MS, and numerical simulations. These data were consistent with a phenomenon where (*SS*)-dimer and (*RRRR*)-tetramer selectively bind the chiral analyte in preference to their enantiomeric counterparts, which ultimately causes them to be amplified and the library to become deracemized.

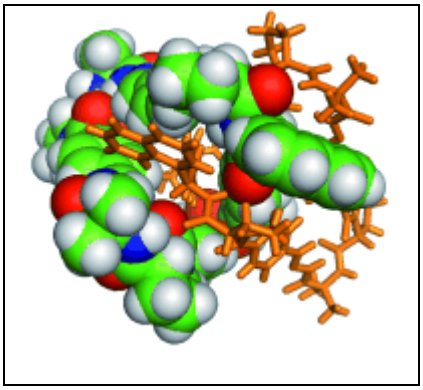


"*The effect of gas-phase reactions on the quantitation of cyclic hydrazone libraries by electrospray ionization (ESI) mass spectrometry*" Holly Schiltz, Mee-Kyung Chung, Stephen J. Lee and Michel R. Gagné *Org. Biomol. Chem.*, **2008**, *6*, 3597-3600.

Using mass spectrometry coupled with LC analysis we report evidence of diastereomer dependent fragmentation and oligomerization reactions in the ionization of acyl-hydrazone-based libraries of cyclic oligomers. These effects can significantly affect the accuracy of MS-based quantitations, but also provide a venue for examining ionization effects in dynamic combinatorial libraries (DCLs).



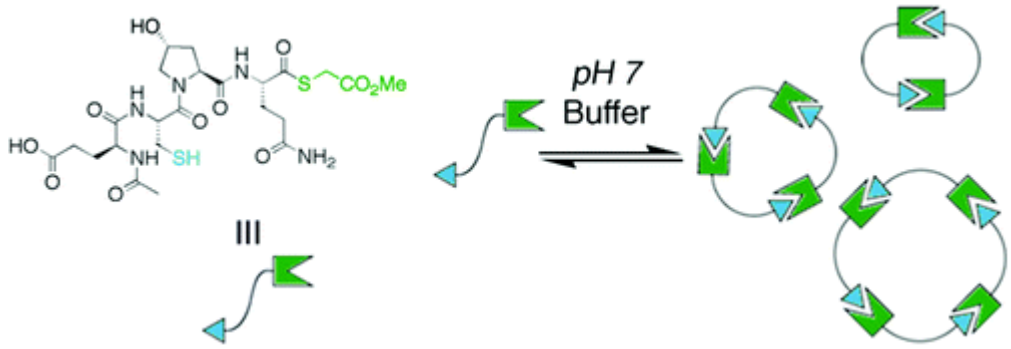
"*Synthesis of Interlocked 56-Membered Rings by Dynamic Self-Templating***"** Mee-Kyung Chung, Peter S. White, Stephen J. Lee, and Michel R. Gagné* *Angew. Chem. Int. Ed*. **2009**, *48*, 8683-8686.



A love of self: Narcissistic macrocyclic rings self-assemble into highly ordered, chiral [2]-catenanes displaying high component diastereoselectivity. The picture shows one such structure. One ring is shown in a space-filling representation, while the other is shown as orange sticks.

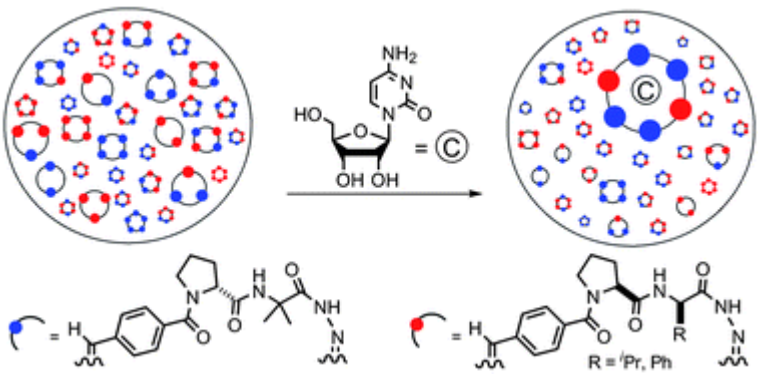
"*Dynamic Cyclic Thiodepsipeptide Libraries From Thiol-Thioester Exchange*" Soumyadip Ghosh, Lindsey A. Ingerman, Aaron G. Frye, Stephen J. Lee, Michel R. Gagné and Marcey L. Waters *Org. Lett.***, 2010**, *12*, 1860–1863.

Thiol−thioester exchange was found to readily generate libraries of cyclic thiodepsipeptides under thermodynamic control, which will enable their use in a variety of dynamic combinatorial chemistry assays. The kinetic determinants of macrocycle formation and the role of amino acid structure on the reaction dynamics are discussed.



"*Constitutionally selective amplification of multicomponent 84-membered macrocyclic hosts for (−)-cytidine•H*$^{+}$" Mee-Kyung Chung, Kay Severin, Stephen J. Lee, Marcey L. Waters and Michel R. Gagné* *Chem. Sci.*, **2011**, *2*, 744-747.

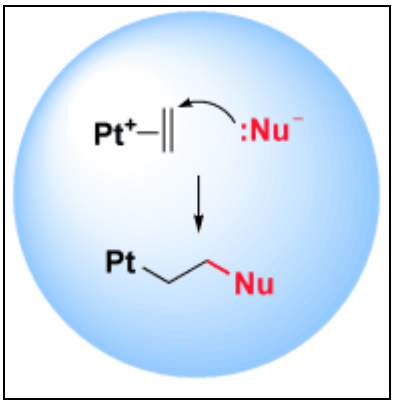
Mixtures of dipeptide monomers create stereochemically and constitutionally complex dynamic libraries of potential receptors. When (−)-cytidine was utilized as guest an 84-membered cyclic host was amplified (70–175 fold) from a nearly undetectable initial concentration. Only the specified diastereomeric combination of the two chiral building blocks yielded a dynamic library from which the macrocyclic receptor could be amplified.



Catalysis

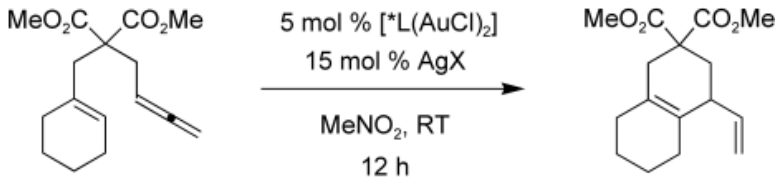
"Electrophilic Activation of Alkenes by Platinum(II): So Much More Than a Slow Version of Palladium(II)" Anthony R. Chianese, Stephen J. Lee, Michel R. Gagné *Angew. Chem. Int. Ed.* **2007**, *46*, 4042-4059.

The electrophilic activation of alkenes by transition-metal catalysts is a fundamental step in a rapidly growing number of catalytic processes. Although palladium is the best known metal for this purpose, the special properties of its third-row cousin platinum (strong metal–ligand bonds and slow substitution kinetics) have enabled the development of transformations that are initiated by addition to the C=C bonds by protic carbon, nitrogen, oxygen, and phosphorus nucleophiles, as well as alkene or arene nucleophiles. Additionally, reactivity profiles, which are often unique to platinum, provide wholly new reaction products. This Review concerns platinum-catalyzed electrophilic alkene activation reactions, with a special emphasis on the mechanistic properties of known systems, on the differences between platinum and palladium catalysts, and on the prospects for the development of new systems.



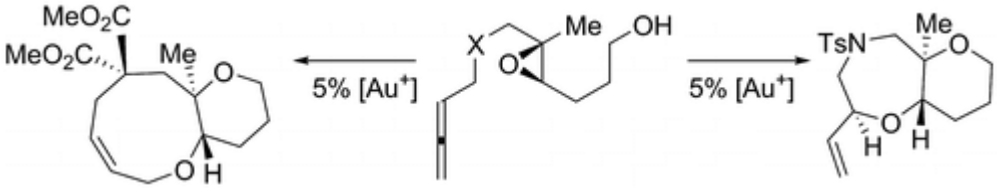
"*Gold(I)-Catalyzed Asymmetric Cycloisomerization of Eneallenes into Vinylcyclohexene*" Michael A. Tarselli, Anthon R. Chianese, Stephen J. Lee, Michel R. Gagné* *Angew. Chem. Int. Ed.* **2007**, *46*, 6670-6673.

Cycloisomerization of eneallenes by cationic gold(I) catalysts produces vinylcyclohexene derivatives in up to 77 % *ee*, using [3,5-xylyl-binap$(AuCl)_2$] and AgOTf additive (see scheme; 3,5-xylyl-binap=2,2′-bis(di(3,5-xylyl)phosphino)-1,1′-binaphthyl). The procedure is amenable to the synthesis of mono- and bicyclic products and is tolerant of ester, alcohol, and amide groups.



"*Gold(I)-Catalyzed Cascade Cyclization of Allenyl Epoxides*" Michael A. Tarselli, J. Lucas Zuccarello, Stephen J. Lee and Michel R. Gagné *Org. Lett.*, **2009**, *11*, 3490–3492.

Cationic gold(I) phosphite catalysts activate allenes for epoxide cascade reactions. The system is tolerant of numerous functional groups (sulfones, esters, ethers, sulfonamides) and proceeds at room temperature in dichloromethane. The cyclization pathway is sensitive to the substitution pattern of the epoxide and the backbone structure of the A-ring. It is capable of producing medium-ring ethers, fused 6-5 bicyclic, and linked pyran-furan structures. The resulting cycloisomers are reminiscent of structures found in numerous polyether natural products.



"*Sn-Free Ni-Catalyzed Reductive Coupling of Glycosyl Bromides with Activated Alkenes*" Hegui Gong, R. Stephen Andrews, Joseph L. Zuccarello, Stephen J. Lee and Michel R. Gagné* *Org. Lett.*, **2009**, *11*, 879–882.

A mild, stereoselective method for the Ni-catalyzed synthesis of α-*C*-alkylglycosides is reported. This approach entails the reductive coupling of glycosyl bromides with activated alkenes at room temperature, with low alkene loading as an important feature. Diastereoselective coupling with 2-substituted acrylate derivatives was made possible through the use of 2,4-dimethyl-3-pentanol as a proton source.